

胆固醇吸收抑制剂联合他汀类药物治疗血脂异常有效性和安全性的网状Meta分析^Δ

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摘要 **目的** 评价胆固醇吸收抑制剂(依折麦布和海博麦布)联合他汀类药物治疗血脂异常的有效性和安全性。**方法** 检索中国知网、PubMed等中英文数据库,收集上述联合用药治疗血脂异常的随机对照试验(RCT),检索时限为建库至2025年10月。筛选文献、提取数据和评价纳入文献质量后,采用R软件进行网状Meta分析。**结果** 共纳入36项RCT。结果显示,在降低低密度脂蛋白胆固醇(LDL-C)、总胆固醇(TC)方面,依折麦布+他汀类药物、海博麦布+他汀类药物均显著优于他汀类药物+安慰剂、安慰剂($P<0.05$),累积排序曲线下面积(SUCRA)排名前2位的均是依折麦布+他汀类药物、海博麦布+他汀类药物;在降低甘油三酯(TG)方面,海博麦布+他汀类药物、依折麦布+他汀类药物均显著优于他汀类药物、他汀类药物+安慰剂、安慰剂($P<0.05$),SUCRA排名前2位的是海博麦布+他汀类药物、依折麦布+他汀类药物;在降低载脂蛋白B(ApoB)方面,依折麦布+他汀类药物显著优于他汀类药物、安慰剂($P<0.05$),SUCRA排名前2位的是依折麦布+他汀类药物、他汀类药物+安慰剂;在升高高密度脂蛋白胆固醇(HDL-C)方面,安慰剂显著优于他汀类药物、海博麦布+他汀类药物、他汀类药物+安慰剂、依折麦布+他汀类药物($P<0.05$),SUCRA排名前2位的是安慰剂、他汀类药物。各干预措施的总不良反应发生率比较,差异均无统计学意义($P>0.05$)。**结论** 依折麦布联合他汀类药物在降低LDL-C、TC及ApoB方面优势显著,海博麦布联合他汀类药物在降低TG方面可能具有潜在优势;两种联合方案的安全性均较好。

关键词 依折麦布;海博麦布;胆固醇吸收抑制剂;血脂异常;他汀类药物;网状Meta分析

Efficacy and safety of cholesterol absorption inhibitors combined with statins in the treatment of dyslipidemia: a network meta-analysis

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ABSTRACT **OBJECTIVE** To evaluate the efficacy and safety of cholesterol absorption inhibitors (ezetimibe and hybutimibe) combined with statins for the treatment of dyslipidemia. **METHODS** Randomized controlled trials (RCTs) about above-mentioned drug combination in patients with dyslipidemia were retrieved from CNKI, PubMed and other Chinese and English databases. The retrieval time limit was from the establishment of the database to October 2025. After screening the literature, extracting the data, and evaluating the quality of the literature, network meta-analysis was performed using R software. **RESULTS** A total of 36 RCTs were included. Results showed that in reducing low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC), ezetimibe+statins and hybutimibe+statins were significantly superior to statins+placebo and placebo alone ($P<0.05$). The top two interventions according to surface under the cumulative ranking curve (SUCRA) rankings were both ezetimibe+statins and hybutimibe+statins. In terms of triglyceride (TG) lowering, both hybutimibe+statins and ezetimibe+statins were significantly better than statins alone, statins+placebo and placebo alone ($P<0.05$), with hybutimibe+statins and ezetimibe+statins ranking top two by SUCRA. For apolipoprotein B (ApoB) reduction, ezetimibe+statins was significantly superior to statins alone and placebo alone ($P<0.05$), and the top two SUCRA rankings were ezetimibe+statins and statins+placebo. In terms of high-density lipoprotein cholesterol (HDL-C) increase, placebo was significantly better than statins alone, hybutimibe+statins, statins+placebo, and ezetimibe+statins ($P<0.05$), and the top two SUCRA rankings were placebo alone and statins alone. There was no statistically significant difference in the overall incidence of adverse reactions among the interventions ($P>0.05$). **CONCLUSIONS** Ezetimibe combined with statins shows significant advantages in reducing LDL-C, TC and ApoB, while the hybutimibe combined with statins may have potential advantages in lowering TG; both combination regimens have good safety.

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significant advantages in reducing LDL-C, TC and ApoB, while the hybutimibe combined with statins may have potential advantages in lowering TG; both combination regimens have good safety.

KEYWORDS ezetimibe; hybutimibe; cholesterol absorption inhibitor; dyslipidemia; statins; network meta-analysis

血脂异常主要定义为脂蛋白胆固醇异常,包括低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、甘油三酯(triglyceride, TG)升高以及高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)降低,这些指标的异常会增加动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD)的发生风险^[1]。

《中国血脂管理指南(基层版2024年)》推荐他汀类药物为血脂异常治疗的初始首选药物^[2]。他汀类药物可通过抑制3-羟基-3-甲基戊二酸单酰辅酶A还原酶,减少胆固醇合成,从而显著降低LDL-C水平,并具有稳定动脉粥样硬化斑块及抗炎等多重作用^[3]。然而,部分患者在使用他汀类药物后,仍无法实现理想的降脂目标,因此联合使用胆固醇吸收抑制剂成为了重要的强化降脂策略^[2]。目前,我国已上市的胆固醇吸收抑制剂有依折麦布和海博麦布。该类物质可通过抑制小肠对胆固醇的吸收,与他汀类药物形成机制互补,进一步降低LDL-C水平^[4-5]。随着他汀类药物的广泛应用,其引起的不良反应逐渐受到临床关注,尤其是肝功能异常、肌病及新发糖尿病等问题,可能影响患者用药依从性及治疗效果^[6-7]。基于此,本研究采用网状Meta分析的方法评价胆固醇吸收抑制剂联合他汀类药物治疗血脂异常患者的疗效和安全性,以期临床决策提供参考。本研究方案已在系统评价预注册中心(PROSPERO)注册,注册号为CRD420251245665。

1 资料与方法

1.1 纳入与排除标准

1.1.1 研究类型

本研究的文献类型为随机对照试验(randomized controlled trial, RCT),语种限定为中文和英文。

1.1.2 研究对象

本研究纳入的患者为血脂异常患者;年龄、种族和性别均不限。

1.1.3 干预措施

试验组患者给予胆固醇吸收抑制剂联合他汀类药物;对照组患者单用安慰剂或他汀类药物或安慰剂联合他汀类药物。胆固醇吸收抑制剂包括依折麦布、海博麦布;他汀类药物包括阿托伐他汀、瑞舒伐他汀等。

1.1.4 结局指标

本研究的主要结局指标为:降低LDL-C百分比;次要结局指标为:降低总胆固醇(total cholesterol, TC)百分比、降低TG百分比、降低载脂蛋白B(apolipoprotein B, ApoB)百分比、升高HDL-C百分比、总不良反应发生率。

1.1.5 排除标准

本研究的排除标准为:(1)重复发表的文献;(2)结局指标不符合的文献;(3)无法获取全文的文献;(4)无法从原文中提取原始数据或数据存在明显错误的文献。

1.2 文献检索策略

检索PubMed、Embase、Cochrane Library、中国知网、维普网、万方数据。英文检索词包括“ezetimibe”“hybutimibe”“hyzetimibe”“HS-25”“randomized controlled trials”;中文检索词包括“依折麦布”“海博麦布”“随机对照试验”。检索时限均为建库至2025年10月。同时,检索文献的参考文献;如有多项文献对同一研究进行报告,则保留涵盖所有指标的文献;若数据缺失则发送邮件咨询通信作者。

1.3 文献筛选与资料提取

由2位研究者独立筛选文献;如遇分歧,则由第3位研究者协助判断。提取信息包括第一作者、发表年份、干预措施、结局指标等。

1.4 纳入文献质量评价

根据Cochrane系统评价员手册5.1.0偏倚风险评估工具对文献质量进行评价,具体包括随机序列产生、分配隐藏、参与者与研究者盲法、结果评估盲法、结局完整性、选择性报告结果以及其他偏倚,每项评为“高风险”“低风险”“不清楚”^[8]。

1.5 统计学方法

使用R软件的“BUGSnet”和“GEMTC”程序包进行网状Meta分析,采用Stata 14.0软件绘制网络证据关系图。当各干预措施形成闭环时,进行不一致性检验,若 $P>0.05$,表明一致性良好,使用一致性模型,反之则采用不一致性模型;若未形成闭合环,表明仅存在间接比较结果,则采用一致性模型。 $I^2<50\%$ 且 $P>0.10$,表示各研究间无统计学异质性,采用固定效应模型;反之,采用随机效应模型。连续型变量以均数差(mean difference, MD)及其95%置信区间(confidence interval, CI)表示,二分类变量以相对危险度(relative risk, RR)及其95%CI表示。采用倒漏斗图进行发表偏倚分析。通过累积排序曲线下面积(surface under the cumulative ranking curve, SUCRA)对各干预措施进行排序:有效性方面, SUCRA值越大,表明疗效越好;安全性方面, SUCRA值越小,表明安全性越高^[9]。检验水准 $\alpha=0.05$ 。

2 结果

2.1 文献检索结果与纳入研究基本特征

初检共检出相关文献4 697篇,经阅读标题、摘要及全文后,最终纳入36篇文献^[10-45],共涉及11 278例患者,其中对照组4 520例、干预组6 758例。结果见图1(限于篇幅,纳入研究的基本信息可扫描本文首页二维码进入“增强出版”板块查看附表1)。

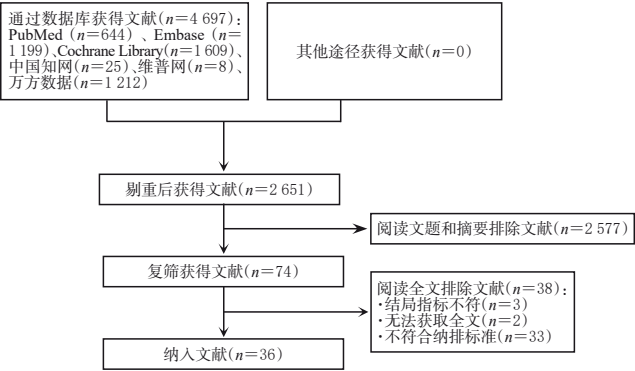


图1 文献筛选流程图

2.2 纳入研究质量评价结果

36项研究中,22项研究提及随机序列生成方法^[10-21,23-24,27,29-30,34-36,39,42];15项研究描述了分配隐藏措施^[10-14,16-21,23-24,27,29];33项研究描述了对参与者和研究者实施盲法以及对结果测评者实施盲法^[10-25,28-36,38-45];所有研究的结局报告均完整、均未选择性报告结果、均无其他偏倚来源(限于篇幅,评价结果可扫描本文首页二维码进入“增强出版”板块查看附图1、附图2)。

2.3 网状Meta分析结果

2.3.1 各结局指标的证据关系

结果显示,除降低ApoB百分比外,其余结局指标的证据关系图均存在闭环。各指标不一致性检验的 P 值均大于0.05,表明各研究一致性良好。异质性检验结果显示,总不良反应发生率在各研究间无统计学异质性($I^2<50\%$, $P>0.10$),采用固定效应模型;其余结局指标在各研究间有统计学异质性($I^2>50\%$, $P<0.10$),采用随机效应模型。结果见图2(以降低LDL-C百分比、降低ApoB百分比为例:直线及线段粗细分别表示进行比较的研究及数量,圆点及其大小分别表示干预措施及对应的样本量)。

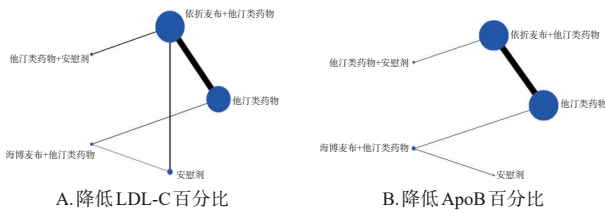


图2 结局指标的证据关系图

2.3.2 降低LDL-C百分比

35项研究报道了降低LDL-C百分比^[10-16,18-45]。结果(图3)显示,在降低LDL-C方面,依折麦布+他汀类药物显著优于他汀类药物、他汀类药物+安慰剂、安慰剂($P<0.05$),海博麦布+他汀类药物显著优于他汀类药物+安慰剂、安慰剂($P<0.05$)。降低LDL-C百分比的SUCRA排序从大到小依次为依折麦布+他汀类药物(98.03%)>海博麦布+他汀类药物(75.07%)>他汀类药物(48.12%)>他汀类药物+安慰剂(28.78%)>安慰剂(0)。

依折麦布+他汀类药物	-2.21(-20.31,15.91)	-7.75(-11.42,-4.10) ^a	-11.35(-21.65,-1.01) ^a	-37.86(-45.72,-30.02) ^a
-5.77(-13.87,2.34)	海博麦布+他汀类药物	-5.53(-23.27,12.18)	-9.14(-30.03,-11.74) ^a	-35.64(-55.36,-15.90) ^a
-12.34(-14.93,-9.80) ^a	-6.57(-14.52,1.35)	他汀类药物	-3.60(-14.54,7.39)	-30.11(-38.82,-21.44) ^a
-16.79(-24.12,-9.43) ^a	-11.02(-21.95,0) ^a	-4.45(-12.20,3.38)	他汀类药物+安慰剂	-26.51(-39.47,-13.54) ^a
-47.85(-53.24,-42.45) ^a	-42.08(-50.69,-33.37) ^a	-35.51(-41.32,-29.58)	-31.06(-40.22,-21.95) ^a	安慰剂

a: $P<0.05$;黄色:降低LDL-C百分比;绿色:降低TC百分比;蓝色:干预措施。

图3 降低LDL-C百分比和降低TC百分比的网状Meta分析结果[MD(95%CI)]

2.3.3 降低TC百分比

33项研究报道了降低TC百分比^[10,12-16,18-19,21-45]。结果(图3)显示,在降低TC方面,依折麦布+他汀类药物显著优于他汀类药物、他汀类药物+安慰剂、安慰剂($P<0.05$),海博麦布+他汀类药物显著优于他汀类药物+安慰剂、安慰剂($P<0.05$)。降低TC百分比的SUCRA排序从大到小依次为依折麦布+他汀类药物(89.53%)>海博麦布+他汀类药物(73.78%)>他汀类药物(50.28%)>他汀类药物+安慰剂(36.39%)>安慰剂(0.02%)。

2.3.4 降低TG百分比

32项研究报道了降低TG百分比^[10-14,16,18-19,22-45]。结果(图4)显示,在降低TG方面,海博麦布+他汀类药物、依折麦布+他汀类药物均显著优于他汀类药物、他汀类药物+安慰剂、安慰剂($P<0.05$)。降低TG百分比的SUCRA排序从大到小依次为海博麦布+他汀类药物(96.59%)>依折麦布+他汀类药物(78.03%)>他汀类药物(49.57%)>他汀类药物+安慰剂(25.82%)>安慰剂(0)。

海博麦布+他汀类药物	0.82(-2.21,3.83)	-0.16(-3.12,2.81)	0.22(-3.88,4.32)	5.47(2.31,8.61) ^a
3.64(-2.61,9.92)	依折麦布+他汀类药物	0.65(-0.33,1.64)	0.60(-2.19,3.37)	6.28(4.43,8.13) ^a
7.12(1.06,13.29) ^a	3.49(1.28,5.74) ^a	他汀类药物	0.06(-2.88,3.01)	5.63(3.58,7.67) ^a
12.80(4.51,21.15) ^a	9.17(3.70,14.66) ^a	5.68(-0.26,11.57)	他汀类药物+安慰剂	5.69(2.36,9.02) ^a
29.90(23.28,36.59) ^a	26.27(22.13,30.42) ^a	22.78(18.14,27.33) ^a	17.10(10.21,23.96) ^a	安慰剂

a: $P<0.05$ 。黄色:降低TG百分比;绿色:升高HDL-C百分比;蓝色:干预措施。

图4 降低TG百分比和升高HDL-C百分比的网状Meta分析结果[MD(95%CI)]

2.3.5 升高HDL-C百分比

33项研究报道了升高HDL-C百分比^[10-16,18-19,21-25,27-45]。结果(图4)显示,在升高HDL-C方面,安慰剂显著优于他汀类药物、海博麦布+他汀类药物、他汀类药物+安慰剂、依折麦布+他汀类药物($P<0.05$)。升高HDL-C百分比的SUCRA排序从大到小依次为安慰剂(99.96%)>他汀类药物(46.90%)>海博麦布+他汀类药物(44.92%)>他汀类药物+安慰剂(40.30%)>依折麦布+他汀类药物(17.91%)。

2.3.6 降低ApoB百分比

25项研究报道了降低ApoB百分比^[10-12,14-16,18-19,22-23,28-30,33-37,39-45]。结果(图5)显示,在降低ApoB方面,依折麦布+他汀类药物显著优于他汀类药物、安慰剂($P<0.05$),他汀类药物+安慰剂显著优于海

博麦布+他汀类药物($P<0.05$)。降低ApoB百分比的SUCRA排序从大到小依次为依折麦布+他汀类药物(86.87%)>他汀类药物+安慰剂(76.83%)>海博麦布+他汀类药物(52.59%)>他汀类药物(31.84%)>安慰剂(1.86%)。

依折麦布+他汀类药物	1.16(0.91,1.46)	1.12(0.87,1.43)	1.01(0.92,1.09)	1.00(0.90,1.11)
2.38(-16.48,21.25)	他汀类药物+安慰剂	1.31(0.91,1.83)	1.17(0.90,1.49)	1.17(0.89,1.50)
11.49(-8.36,31.40)	9.11(-18.34,36.47) ^a	海博麦布+他汀类药物	1.12(0.88,1.41)	1.12(0.84,1.46)
17.56(11.84,23.27) ^a	15.18(-4.55,34.83)	6.06(-12.98,25.11)	他汀类药物	1.01(0.87,1.15)
45.52(12.00,79.28) ^a	43.14(4.69,81.90) ^a	34.03(7.12,61.08) ^a	27.96(-5.05,61.08)	安慰剂

a: $P<0.05$ 。黄色:降低ApoB百分比;绿色:总不良反应发生率;蓝色:干预措施。

图5 降低ApoB百分比[MD(95%CI)]和总体不良反应发生率[RR(95%CI)]的网状Meta分析结果

2.3.7 总不良反应发生率

30项研究报道了总不良反应发生率^[10-12,14-21,23-24,26-29,32-37,39-45]。结果(图5)显示,各干预措施的总不良反应发生率比较,差异均无统计学意义($P>0.05$)。总不良反应发生率的SUCRA排序从大到小依次为他汀类药物+安慰剂(88.50%)>依折麦布+他汀类药物(50.54%)>安慰剂(47.91%)>他汀类药物(46.38%)>海博麦布+他汀类药物(16.66%)。

2.4 发表偏倚分析

各指标所得倒漏斗图对称性较好,但部分散点分布在倒漏斗之外,提示可能存在发表偏倚。结果见图6(以降低LDL-C百分比为例)。

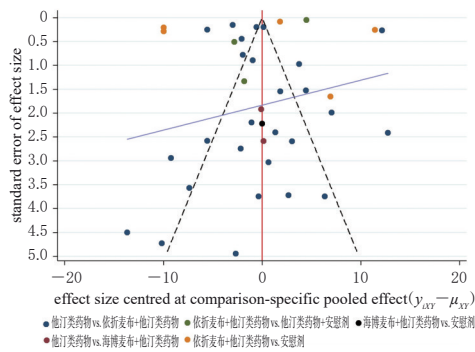


图6 降低LDL-C百分比的发表偏倚分析

3 讨论

本研究结果显示,依折麦布联合他汀类药物在降低LDL-C、TC及ApoB方面均表现出显著优势,其SUCRA排名均居首位。这提示,该联合方案在改善动脉粥样硬化相关脂质指标方面具有较高的综合获益。LDL-C是ASCVD发生和发展的关键危险因素,已有研究证实,LDL-C水平与心血管事件风险显著相关^[2]。依折麦布可抑制人胆固醇转运蛋白NPC1L1介导的肠道胆固醇吸收,与他汀类药物能抑制胆固醇内源性合成形成互补机制,使LDL受体表达上调,从而实现协同降脂效果^[46],该机制也进一步证明了本研究结果的可靠性。

本研究中,海博麦布联合他汀类药物在降低TG方

面具有显著优势,其SUCRA排于首位。海博麦布改善TG的优势可能与其药代动力学特征及对脂质转运通路的影响有关^[4]。对于伴有高TG血症的血脂异常患者,海博麦布联合他汀类药物可能是一种具有潜在价值的治疗选择,但仍需更多直接比较研究进一步验证。

在改善HDL-C方面,本研究未观察到依折麦布或海博麦布联合他汀类药物的明显优势,安慰剂在SUCRA排名中居首位。这提示,无论是依折麦布还是海博麦布,对升高HDL-C的作用有限。近年来有研究认为,单纯提高HDL-C水平与心血管获益无关^[47]。

在安全性方面,各干预措施的总不良反应发生率比较,差异均无统计学意义。这提示,依折麦布或海博麦布联合他汀类药物的总体耐受性良好。SUCRA排序结果显示,海博麦布联合他汀类药物的安全性最高,虽然依折麦布联合他汀类药物的排名相对靠后,但仍未明显增加总不良反应的发生风险。这提示,依折麦布或海博麦布联合他汀类药物的安全性较好。

本研究存在一定局限性:(1)部分纳入研究为开放性设计,可能存在一定实施偏倚;(2)不同研究在他汀类药物种类、剂量、疗程及研究人群特征方面存在差异,可能使结果产生一定异质性;(3)本研究主要关注血脂指标变化,未直接评估心血管终点事件,使长期临床获益评估受限。

综上所述,依折麦布联合他汀类药物在降低LDL-C、TC及ApoB方面优势显著,海博麦布联合他汀类药物在降低TG方面可能具有潜在优势;两种联合方案的安全性均较好。

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